

This is an open label, Phase Ia/Ib study to evaluate the administration of a DNA vaccine by in vivo electroporation in patients at high risk for recurrence of metastatic melanoma. The objectives of the study are to characterize the safety and immunogenicity of a DNA vaccine encoding the mouse tyrosinase gene (pINGmuTyr) delivered by in vivo electroporation in patients with American Joint Council on Cancer (AJCC) stage IIB-IV malignant melanoma that are HLA-A1, A2, A24, or B35 positive. The nature, frequency, and severity of any toxicity associated with vaccination will be assessed in order to determine a Maximum Tolerated Dose (MTD) of pINGmuTyr delivered using Ichor Medical System's device for electroporation mediated intramuscular delivery. Once a MTD has been established, enrollment will be expanded to assess the effect of electroporation mediated delivery of the DNA vaccine on generation of immune response to tyrosinase.

The hypothesis to be evaluated in the proposed study is: A regimen of five immunizations with a xenogeneic tyrosinase DNA vaccine (pINGmuTyr) administered by in vivo electroporation will be safe and will induce immune responses specific for tyrosinase in patients with stage IIB-IV malignant melanoma.

The hypothesis will be evaluated using a single arm open label study design. All subjects will receive the study vaccine administered by in vivo electroporation; there is no placebo. A total of up to 27 patients will be enrolled in the study. The pINGmuTyr vaccine will be administered at one of three dose levels (0.2 mg, 0.5 mg, or 1.5 mg). pINGmuTyr will be administered at Weeks 1, 4, 7, 10, and 13. The proposed dose levels and administration frequency are based on those evaluated in a previous clinical trial of intramuscular delivery of the pINGmuTyr DNA vaccine (MSKCC IRB#:99-122A(1)).

The goal of the Phase Ia portion of the study will be to define a MTD of pINGmuTyr given by electroporation within the dose range under evaluation. Enrollment will be initiated at the 0.2 mg dose. Initial enrollment at each dose level will comprise a cohort of up to three patients. Subsequent patient enrollment and a determination of the MTD will be based on characterization of the occurrence of Dose Limiting Toxicity (DLT).

Once the MTD has been established, the Phase Ib portion of the trial will be initiated. Enrollment will be expanded at the MTD until a total of 15 patients have been accrued at this pINGmuTyr dose level. The objective of the Phase Ib portion

of the study will be to characterize the frequency and magnitude of tyrosinase specific immune responses observed following electroporation mediated pINGmuTyr delivery in the study population.

Subject evaluations will include post-administration monitoring, physical exams, evaluation of blood chemistry and hematology. Patients' sera and peripheral blood mononuclear cells will be collected in order to measure the antibody and T cell responses induced by the vaccines. Specifically, titers of IgM and IgG antibodies against mouse tyrosinase will be measured for serological response and Elispot assays for CD8+ T cell responses will be assessed.